EXPERIENCES WITH RHEUMATIC FEVER IN THE ARMY*

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AN attempt to crystallize the status of experience with rheumatic fever at this time is fraught with hazard, yet such attempts seem warranted even if their main function remains but to challenge previous conceptions and to raise new questions. The opinions expressed in this paper are those of the author and are not shared by all workers in this field. They are not to be construed as representing official pronouncements of the Office of The Surgeon General.

Rheumatic fever, as most physicians knew it prior to the war, was largely an endemic disease with sporadic, but relatively rare epidemics of minor proportions. It was not considered to be highly communicable. Numerous publications contended that the major etiological factors were malnutrition, poor heating, and other problems of the underprivileged classes. By far, the majority of cases developed in children and adolescents. It has always been a potentially very serious disease for the affected patient.

It is a serious problem for the military forces, both because of the immediate long hospitalization and because of the danger of the effects which may invalid these patients for years later in life. In several areas it has assumed epidemic proportions. These have been most pronounced in camps in the Rocky Mountain and Central states. In some barracks it has reached a much higher incidence than would have been anticipated in this age group, on the basis of former experience.

The curve of incidence has, in general, diminished with increasing age. The oldest patient seen by the author, having his first attack while in an Army hospital, was 42 years of age.

The military personnel with this disease have not been emaciated, undernourished, or in poor physical condition. On the contrary, they represent, in most instances, the cream of our youth, physically and

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mentally. They are in splendid physical training. Those stricken in this country have been on plentiful diets which were, for the most part, very well planned. Some of the men who developed rheumatic fever overseas have been on field rations for from one to five months. Heavy physical exercise with resulting fatigue has been frequent, but not invariable before onset. Exposure to prolonged dampness and cold has appeared to precipitate many atacks, but again has not been an invariable prefatory occurrence.

Close contact in living quarters has been a most consistent environmental factor, as it almost invariably must be, in the spread of the disease since practically all attacks of rheumatic fever are preceded by Group A hemolytic streptococcal infections of the respiratory tract. Evidence is increasing that the lesions of rheumatic fever may be the results of an anaphylactic reaction to some foreign antigen, such as a product of the hemolytic streptococcus.[1,2] This applies to the reaction of rheumatic pneumonitis[3] as well as joint and skin manifestations.

Characteristically, in the Army camps the curve of increase in the incidence of rheumatic fever has been preceded by a curve of increased incidence of upper respiratory infections. Where bacteriological studies have been made, these have been predominantly Group A Streptococcus infections. On the other hand, many waves of upper respiratory infections have not been followed by any increase in rheumatic fever. This has been previously observed in relation to the Autumnal epidemics of "colds" along the Eastern seaboard.

In general, the Army cases have followed the usual course of events as outlined by Swift[4] namely:

Phase I.—An upper respiratory streptococcal infection, either a nasopharyngitis, follicular tonsillitis, or scarlet fever.

Phase II.—A quiescent phase, which may be considered as an incubation period, and

Phase III.—The phase of rheumatic activity, which may continue in duration from a few weeks to years.

Actually the first two phases frequently escape detection, or are quickly forgotten, so that only careful questioning will reveal even an approximately accurate rate of incidence. These two phases are, nevertheless, of greatest importance since most patients convalescing from *streptococcus* tonsillitis, or nasopharyngitis are below par physically, and being candidates for rheumatic fever and other serious diseases

should not be exposed at too early a date to too great cold, dampness, or fatigue.

The second phase may pass immediately into the third or active rheumatic fever phase, or it may take as long as six to seven weeks. Most of the serious complications can be detected by having the patients under observation between the fifteenth and twentieth days after the onset of Phase I. In military establishments this is not always feasible, but proper instructions can be issued to the soldier so that suspicious symptoms or signs developing during that time will be brought immediately to the attention of the medical officer.

The history of previous attacks has been very common. In one ward in an Induction Center Station Hospital of twenty-eight patients who had developed rheumatic fever within thirty days of their entrance into the service, eighteen had had a previous history of one or more previous attacks from one to fourteen years before. Most of these men had done fairly well in the protected environment of civilian life, but even a brief trial with exercise and exposure to which they were unaccustomed resulted in reactivation of their disease. Ten of them had no history suggestive of the first phase of upper respiratory infection.

This gives rise to the following question: Is this new attack, thus precipitated, due to hidden foci of streptococci Group A; or is it due to reactivation of a latent anaphylactic process secondary to the stimuli of fatigue, exposure to inclement weather, or upper respiratory infections, any one of which may act as the trigger mechanism initiating the process?

It has been difficult, and even impossible at times, to differentiate the pseudo from the true rheumatic fever syndrome. The confusing signs include tachycardia, substernal distress, dyspnea on exertion, pronounced arthralgia, and backache, without local redness, heat, or swelling of the soft parts. If not due to true rheumatic fever, these are usually considered to be on the basis of toxicity (though we do not know exactly what we mean by that term), and disappear with the general improvement of the patient.

Most of the patients in the military services have followed the usual course during the active rheumatic fever phase. Several points, however, are worthy of note. In more than 1000 patients, there have been only three who have had chorea at any time, during their Army serv-

ices. In no case has it occurred as an isolated manifestation of rheumatic fever. This is remarkably lower than the incidence of chorea in rheumatic fever in pre-war civilian practice.

The characteristic painful, swollen, red, hot joints have varied greatly in shifting tendencies and in severity. The cardiac manifestations have included precordial discomfort, tenderness on pressure, pain, dyspnea, tachycardia, premature contractions, fibrillation, and flutter. Heart block varied from partial to complete with ventricular rates as low as 20 per minute. This will be discussed later in this paper.

The hearts have rarely been slightly enlarged with the first attack. On auscultation the first sign of change has most frequently been a muffled soft *systolic blowing murmur* over the mitral area with a fairly wide distribution. This has frequently disappeared on change of position such as sitting upright, and may disappear completely with subsidence of the acute phase of the disease, in which case it may be difficult to be certain whether it was evidence of an organic or functional process. Although the fashion of the day is to arbitrarily classify many such murmurs as functional, it would seem advisable to be less positive since the post-mortem findings have embarrassed the clinician more than once in this regard. *Diastolic* and *presystolic* murmurs in this area are more safely classified as organic. In some instances, a *mid-diastolic rumbling murmur* has developed two to three months after the initial rheumatic fever attack. Several of these have later become inaudible. The explanation for this is not clear. The most common *murmur in the aortic area* has been soft, blowing, and *diastolic* heard loudest over the second and third right interspace. It probably represents a relative insufficiency in the majority of patients and frequently, but not always, disappears. The murmurs of mitral and aortic stenosis tend to develop later, and were with few exceptions, encountered only in patients with previous history or evidence of rheumatic fever.

Pericarditis, while not common, has occurred frequently enough to be worthy of constant consideration. Most of these patients developed their pericardial signs within a few days of the onset of the active rheumatic fever phase, often before therapy had reached an intensive phase. The lack of reliability of statistical studies in this regard was recently brought forcibly to my attention by the following incident: Two hospitals drawing from the same pool of personnel each had approximately seventy-five patients with rheumatic fever. One had no

patients with pericarditis, the other had eight patients with pericarditis. In each of these the pericarditis developed within the first four to five days of onset of recognized rheumatic fever.

Heart failure has been very rare during the first attack, having been encountered in only five patients in this series. Changes in the electrocardiogram will be discussed below.

It must never be forgotten that abdominal symptoms may represent the onset of rheumatic fever. Pain, tenderness, rebound tenderness, and cramps have been frequent and have led to confusion with the diagnosis of appendicitis.

Of particular note has been the scarcity of subcutaneous nodules—only four examples have been seen in more than 1000 cases. Purpura has been rare. The reason for this is not understood. Of possible significance in this regard is the recent work of Link[5] and others demonstrating that salicylates may produce hemorrhage. This occurs only in the presence of a Vitamin K deficiency and is prevented by adequate Vitamin K in the diet. This may, in part, explain the tendency toward hemorrhage noted in underprivileged children and its absence among well nourished troops. It has further been noted[5] that sodium salicylate, which is used in the Army, produces less tendency toward reduction of the prothrombin level than acetyl salicylic acid—commonly used in civilian practice.

We have seen eight examples of cerebral manifestations; five simulating meningitis and three developing a transient psychosis. In these three the question of salicylism was considered. In this series, there have been seven fatalities. Two were associated with pericarditis, and five with heart failure. All of these had histories of previous attacks of rheumatic fever. Four of the latter five had pneumonia which, in two instances, was shown pathologically to resemble rheumatic pneumonitis as described by Rich and Gregory.[3] Numerous additional patients developed what was diagnosed as primary atypical pneumonia, but which was probably in some cases, rheumatic pneumonitis. This possibility should be constantly kept in mind in treating patients with rheumatic fever.

Electrocardiographic changes have been of great interest. The most consistent change was prolongation of the P-R interval—the longest seen being 0.62. This finding is often the only evidence of heart involvement and is usually transient, disappearing in from one to six

months. Partial A-V heart block with the Wenckebach phenomenon and dropped beats has occurred in approximately 6 per cent of the cases. Auricular ventricular dissociation has occurred with equal frequency.

Prolongation of the P-R interval was found in fifteen out of two hundred patients suffering from what was considered to be typical rheumatoid arthritis, at the Army and Navy General Hospital. Aschoff bodies have been found in the hearts of many patients who died after years of so-called typical rheumatoid arthritis. The prolonged P-R intervals added additional evidence to the hypothesis that, in many instances, these diseases are closely related or run concurrently in susceptible individuals.

The question inevitably arises as to whether we are detecting all of the changes which takes place in the heart. Wendkos[6] has contributed suggestive information to this field by the following study: Eight men suffering from acute migratory polyarthritis (typical of rheumatic fever), in whom no evidence of heart damage existed, showed normal electrocardiographic tracings. Immediately after a controlled tracing, 0.5 Mgm. of ergotamine tartrate (a sympathicolytic drug) was injected intravenously in each. Further tracings were recorded thirty and sixty minutes after injection. Additional tracings were taken of five patients after all evidence of activity of the disease had subsided. The results were as follows: The control tracings in each instance were normal. In six of the eight cases the tracings taken after the injection of ergotamine showed significant disturbances in rhythm usually associated with rheumatic fever, consisting of first degree A-V heart block in four instances, second degree A-V heart block with dropped beats in one instance and nodal rhythm with first degree A-V block in another. The maximum effect was noted in thirty minutes and the effects had generally disappeared within sixty minutes. In the five individuals, who were rechecked after the active phase of the disease had subsided, no alterations from normal, except for slight slowing of the sinus rate could be produced by the same experiment. They had returned to the state of reactivity which characterized normal hearts checked by this method.

If this work is substantiated by additional studies, it would appear to offer a means of sensitizing our technique for the detection of cardiac involvement in rheumatic fever. We do not as yet know whether other

TABLE I (From Wendkos)

CHANGES IN THE ELECTROCARDIAGRAM FOLLOWING THE ADMINISTRATION OF ERGOTAMINE

Case No.	*Age*	*Date*	*Response to Ergotamine*	*Remarks*
1	24	2-14-44	Second degree A-V heart block with dropped beats	Rapid sedimentation time Joint pains present
1	24	3-25-44	Some slowing of sinus rate	Normal sedimentation time Joint pains absent
2	21	1-24-44	Nodal rhythm with first degree A-V heart block	Rapid sedimentation time Acute polyarthritis
2	21	3-1-44	Some slowing of sinus rate	Normal sedimentation time Joint pains absent
3	19	12-10-43	First degree A-V heart block (PR-0.28)	Rapid sedimentation time Acute polyarthritis
3	19	3-10-43	Some slowing of sinus rate	Normal sedimentation time Joint symptoms absent
4	21	3-12-44	First degree A-V heart block (PR-0.40)	Rapid sedimentation time Joint pains both shoulders
4	21	3-23-44	Some slowing of sinus rate	Sedimentation time reduced Joint pains absent
5	19	3-12-44	First degree A-V heart block (PR-0.32)	Acute polyarthritis Sedimentation time rapid
5	19	3-18-44	Some slowing of sinus rate	Arthritis completely disappeared Sedimentation time reduced
6	34	1-3-44	First degree A-V heart block (PR-0.30)	Sedimentation time rapid. Acute polyarthritis with some persistent deformity and swelling in small joints of hand

infectious diseases can produce a similar reaction, or whether such a reaction can be elicited during the toxic period of the first, or upper respiratory phase of rheumatic fever.

It has previously been demonstrated that a parasympathicolytic drug such at atropine can temporarily abolish the first degree A-V heart block and other types of rhythm disturbances, which are the chief electrocardiographic expressions of the disease. This work with ergotamine tartrate suggests that subordination of a hypervagotonic state below a critical level will prevent the registration of the usual electrocardiographic pattern of this dysfunction. The depression of the normal antagonist of the vagus by the use of a sympathicolytic preparation

such as ergotamine tartrate may permit the latent phase to register existing changes in the electrocardiogram. Further studies of this phenomenon may yield worthwhile information and aid us to evaluate more accurately the extent of involvement of the heart during the acute phase of the disease. The degree of *permanent* damage in mild cases still eludes our best efforts.

Other transient changes in the electrocardiogram have been frequently observed. These include inversion of the QRS complex and diminution or inversion of the T wave, especially in lead 4. Serial electrocardiographic studies revealing elevation of all or most of the S-T segment, followed by inversion of T waves in multiple leads have been suggestive of pericarditis with an active inflammatory process in the subepicardium. In 18 per cent of a series upright T waves exceeding 10 Mm. occurred in lead CF_4.[7] Wandering pacemakers were encountered in a small number of cases.

The Chemotherapeutic Aspects of the Treatment of Rheumatic Fever

While no completely satisfactory therapy is available for rheumatic fever, the attack has been actively pressed in the military hospitals. Penicillin is now recognized to be of no value in combating this disease.[8,9] The therapeutic use of the sulfonamides has likewise been disappointing. The prophylactic use of sulfonamides will be discussed below. The streptococcus antisera have been without value.

The most interesting contributions to therapy have dealt with the use of salicylates, which have entertained varying degrees of popularity during the past years. A very definite step forward was taken by Brodie, Udenfriend and Coburn in establishing a method for determining the level of salicylic acid in the plasma.[10] This at least makes it possible to be certain that adequate absorption takes place by whatever method of administration is used. While there may be some correlation between the level of salicylates in the plasma and the therapeutic response, there is a considerable variation in this which may be due to (a) a difference in response of the antigen or the inflammatory reaction in different hosts, (b) to the possibility that the level in the blood may not always bear a direct relationship to the level, or utilization in the affected tissues themselves. Further work will help to clarify this point.

The use of larger doses of salicylates orally and intravenously has

been advocated by Coburn and others. This has stimulated more careful observations of the use of these large doses and certain facts and questions have evolved. We have found that most of our patients can tolerate, without serious inconveniences, doses of salicylates which we formerly hesitated to prescribe. A dose of 6 to 8 grams daily was formerly considered to be a large dose. Coburn suggested 10 gms. (150 grs.) as an average, seeking to maintain a level of 35 mg. per 100 cc. or higher. I have seen 20 gms. (300 grs.) given daily to certain patients without detectable untoward effects. Perhaps this tolerance for the drug is related to the splendid physical condition of the men at the onset of the disease and to the diets which they have received containing adequate vitamin K. At present, this must remain speculation. The problems of salicylism will be discussed later.

Agreement has been reached regarding the value of salicylates administered orally, but the determination of additional value following intravenous administration is still debated. The action of salicylates is, in all probability, not upon the infectious agent but rather upon the sterile inflammatory reaction which occurs during activity of the rheumatic process. The evaluation of therapeutic response is determined by clinical improvement and the curve of the sedimentation rate which is generally accepted as being of great value in following the course of this disease.

Early reports suggested that the administration of 10 gms. of sodium salicylate per day intravenously for 6 to 8 days followed by the oral administration of equal doses would result in a rapid subsidence of clinical activity and a drop in the sedimentation rate to within normal within fourteen days. Most of our patients have responded very well clinically to rest in bed and from 10 to 12 gms. of salicylate daily without intravenous therapy.

The evidence at present seems to indicate that intravenous administration has no advantages over oral administration, with the possible exception of rapidity of rise in the blood level. If this route is to be used at all, salicylates should be given intravenously only to very acutely ill patients and patients with evidence of early pericarditis. There is considerable doubt that it is ever necessary.

The response of the sedimentation rate to both intravenous and massive oral dosage has been disappointing having, in a large proportion of our patients, failed to approach normal until the third to the

sixth week of the treatment. This lag has occurred in spite of blood levels of 35 mg. per 100 cc. or more.

The use of the large dose technique with blood levels of 35 mg. or higher does not offer complete protection against pericarditis. I have seen four patients who developed pericarditis during intravenous therapy.

Comparable series were studied in one hospital with the intravenous technique (10 gms. daily) followed by 10 to 16 gms. orally of sodium salicylate daily and with oral administration alone.

Of twenty-nine patients treated initially by intravenous technique, six had probable or definite heart disease before this attack (based on a history of rheumatic fever and presence of a cardiac lesion). Twenty developed evidence of a cardiac lesion during the period of observation as judged by either progressive electrocardiographic changes or the development of what were considered to be significant murmurs. Nine did not. Five of the new patients showed persistent evidence of cardiac residua in the form of significant murmurs. Eleven showed no residua. On thirteen, the late follow-up was unsatisfactory.

Of twenty-nine patients treated throughout by oral administration of 10 gms. daily, seven had cardiac disease before the present attack, eighteen developed signs during this episode, five of these showed persistent cardiac residua, nineteen showed none, and on five, the follow-up was unsatisfactory. In reference to cardiac lesions, the results were, therefore, not strikingly different in these small series.

While there exists serious doubt regarding the merits of intravenous over oral methods of administration, there is practically universal agreement that massive dosage (10 gms. or more) given by either route has produced more uniformly satisfactory palliative results than the smaller doses formerly employed. Many patients can be cited in whom the clinical course including the sedimentation rate improved strikingly with elevation of the plasma salicylate level but in whom the relapses occurred when the plasma level was allowed to drop below 20 mg. per 100 cc. Sharp evidence that this problem is far from solved was presented by one series of sixty-four patients receiving massive dosage therapy by mouth of whom twenty-nine or 45 per cent developed persistent valvular heart lesions.

One of the complications which has been more prominent following the use of such large doses of salicylates is acute salicylism. Some patients

can tolerate levels of 60 mg. per 100 cc. without symptoms but many of our patients develop mild symptoms at a level between 25 and 35 mg., and the percentage increases with the elevation of the level. Beginning with tinnitus, colored vision, nausea, and vomiting, this may progress to a more severe phase of which hyperventilation is a warning signal. This may increase in depth and intensity to simulate Kussmaul breathing. This hyperpnea produces a respiratory (paradoxical) alkalosis which results in lowered CO^2 content of the serum, loss of base (sodium) from the serum via the urine; retention of chloride in the serum; decreased renal function with retention of water, numbness, tingling of extremities, and tetany with carpopedal spasm and positive Chvostek's sign. An acute maniacal delirium may accompany this picture or develop as an isolated reaction.

Mild or moderate salicylism is not of serious significance. If severe with a serum salicylate level of under 50 mg. per 100 cc., one or two liters of normal saline intravenously with sodium bicarbonate, 0.6 gms. every four hours by mouth is usually adequate. If the level is over 50 mg. the salicylate should be stopped and one to five liters of normal saline given intravenously slowly. This toxicity can be prevented in practically all cases by a dose of 0.9 gms. of sodium bicarbonate with each dose of salicylate.[11] On the other hand, it has been shown by Smull, Wégria, and Leland,[12] that the administration of therapeutically satisfactory doses of sodium bicarbonate definitely decreases the level of salicylates in the blood. We must apparently, by balancing the administration of these two substances, tread between the maximum therapeutic effect and the toxic level, and this zone may differ considerably in different individuals.

For the reasons presented above, salicylic acid cannot be considered the final solution to the therapeutic problems occurring in rheumatic fever. The objectives can be clearly stated. A drug must be found which: 1) is non-toxic in effective therapeutic doses, 2) modifies the immune response of the host so that the patient recovers promptly after a monocyclic attack, or 3) inhibits the capacity of the infecting micro-organism to elaborate antigen. In the absence of fulfillment of any of these objectives we are limited at present to the action of the salicylates in suppression of the inflammatory process.

The possibility of prophylaxis of rheumatic fever with sulfonamides has been the subject of much thought and study. These drugs are of no

value in the treatment of the acute phase of the disease. Figures have been presented on numerous occasions supporting the thesis that small doses of sulfanilamide (0.5-1.0 gm.) taken daily will markedly decrease the incidence of recurrences of rheumatic fever after the first attack. Statistically, some of these figures have been subject to question.

Some of the patients have now taken this dosage for several years. This interminable program is not feasible as a preventive measure for use with groups of thousands of troops merely because they happen to be located in an area with a high rate for rheumatic fever. Methods have been used whereby varying dosages have been administered, i.e., 4 gms. sulfadiazine in 48 hours, 6 gms. in 72 hours, and 1 gram daily for a period of weeks. The rates of upper respiratory diseases can apparently be very favorably affected,[13] especially by the last named dose. This can be anticipated in those that are associated with streptococcus infections.

Scarlet fever and meningococcus infections are likewise favorably affected by the sulfonamides prophylactically. The evidence for the long-term effect on rheumatic fever of these small doses over short intervals is to date suggestive,[14] but less conclusive and must await further work.

Fear has been expressed that the early use of sulfonamides after the acute phase of rheumatic fever might unfavorably affect the course of the disease even causing relapses. Under our direction one gram of sulfadiazine has been given to each of twenty-five patients daily for twenty-one days beginning on the fifth day after the temperature had reached normal, regardless of the level of the sedimentation rate. In no instance was any elevation of the sedimentation rate or change in symptomatology noted which could be attributed to the administration of the sulfadiazine; therefore, although the possibility cannot be denied, it seems that risk on this basis is probably not excessive. Further studies on this problem are being carried out. The risk of sulfonamide sensitization must be considered in mass treatment. After sensitization has occurred, skin reactions are not uncommon and we have seen two acute deaths which appeared to be of an anaphylactic nature.

Comments and Conclusions

Rheumatic fever, as it occurs in the Army, has been demonstrated to be a manifestation of a highly communicable disease complex which

frequently is preceded by an outbreak of upper respiratory infections. Evidence is accumulating that it is an anaphylactic reaction, probably to the streptococcus Group A. This is not, however, conclusively established as yet. It may be widespread in its attack on well-nourished young men believed to be in excellent physical condition. The greatest involvement has been among the *younger groups* of servicemen. Fatigue, exposure to cold and dampness, and close living quarters are believed to be important environmental factors. Patients with a previous history of rheumatic fever are especially susceptible to recurrences when exposed to the rigors of military life.

The symptoms, physical findings, laboratory and electrocardiographic changes have been presented. The rarity of subcutaneous nodules, purpura, and chorea is of especial interest. The occurrence of prolongation of the P-R interval and of Aschoff bodies in the hearts of patients with "so-called" typical rheumatoid arthritis of many years standing has been confirmed. The possibility of sensitizing our methods of determining latent damage to the conduction mechanism of the heart by the use of ergotamine tartrate has been discussed.

The present status of the treatment of rheumatic fever remains unsatisfactory. Penicillin and the sulfonamides have been proven to be valueless in the treatment of this disease. There is no evidence that penicillin is of value as a preventive. Prolonged daily dosage of sulfanilamide appears to lessen the frequency of recurrences.[14] The evidence that short courses of sulfonamides are of long term value in the prophylaxis of primary or recurrent attacks of rheumatic fever is suggestive, but not as yet conclusively established. It is possible to markedly reduce the rate of upper respiratory infections, especially those associated with certain strains of streptococci by this method.

A step forward has been taken in the treatment of rheumatic fever with the development of a method for determining the level of salicylates in the blood thus aiding in the control of the dosage. It is fairly well agreed that large doses of sodium salicylate, i.e., 10 gm. daily or more are more rapidly palliative than the formerly used smaller doses. It is highly doubtful that the intravenous administration of salicylates is of greater value than oral administration. The clinical response to large doses has been rapid, but the response of the sedimentation rate has in many of our cases been disappointingly slow. The use of the massive dose methods does not offer complete protection against pericarditis,

myocarditis, or endocarditis.

With massive doses salicylism must be watched for. It can be prevented by giving sodium bicarbonate with the sodium salicylate, but it should be appreciated that this will result in a lowering of the blood level of the salicylates. The effect which this may have on the efficiency of the salicylates has not been established.

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